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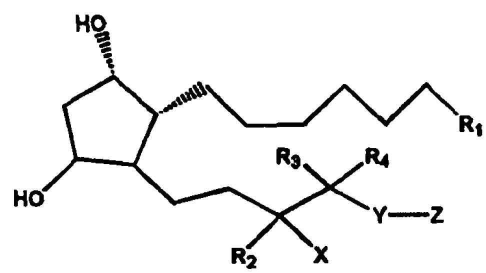
(54) Title: AROMATIC C_{16}–C_{20}–SUBSTITUTED TETRAHYDRO PROSTAGLANDINS USEFUL AS FP AGONISTS

(57) Abstract

The invention provides novel PGF analogs. In particular, the present invention relates to compounds having a structure according to formula (A), wherein R_1, R_2, R_3, R_4, X, Y and Z are defined below. This invention also includes optical isomers, diastereomers and enantiomers of said formula, and pharmaceutically-acceptable salts, biohydrolyzable amides, esters, and imides thereof. The compounds of the present invention are useful for the treatment of a variety of diseases and conditions, such as bone disorders and glaucoma. Accordingly, the invention further provides pharmaceutical compositions comprising these compounds. The invention still further provides methods of treatment for bone disorders and glaucoma using these compounds or the compositions containing them.



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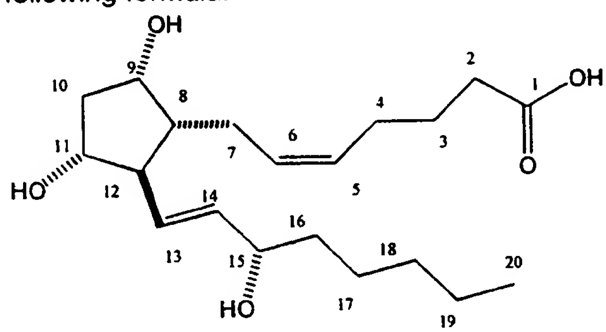
AROMATIC C_{16} - C_{20} - SUBSTITUTED TETRAHYDRO PROSTAGLANDINS USEFUL AS FP AGONISTS

TECHNICAL FIELD

The subject invention relates to certain novel analogs of the naturally occurring prostaglandins. Specifically, the subject invention relates to novel Prostaglandin F analogs. The subject invention further relates to methods of using said novel Prostaglandin F analogs. Preferred uses include methods of treating bone disorders and glaucoma.

BACKGROUND OF THE INVENTION

Naturally occurring prostaglandins (PGA, PGB, PGE, PGF, and PGI) are C-20 unsaturated fatty acids. $PGF_{2\alpha}$, the naturally occurring Prostaglandin F in humans, is characterized by hydroxyl groups at the C_9 and C_{11} positions on the alicyclic ring, a cis-double bond between C_5 and C_6, and a trans-double bond between C_{13} and C_{14}. Thus $PGF_{2\alpha}$ has the following formula:



$PGF_{2\alpha}$

Analogs of naturally occurring Prostaglandin F have been disclosed in the art. For example, see U.S. Patent No. 4,024,179 issued to Bindra and Johnson on May 17, 1977; German Patent No. DT-002,460,990 issued to Beck, Lerch, Seeger, and Teufel published on July 1, 1976; U.S. Patent No. 4,128,720 issued to Hayashi, Kori, and Miyake on December 5, 1978; U.S. Patent No. 4,011,262 issued to Hess, Johnson, Bindra, and Schaaf on March 8, 1977; U.S. Patent No. 3,776,938 issued to Bergstrom and Sjovall on December 4, 1973; P.W. Collins and S. W. Djuric, "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs", Chem. Rev. Vol. 93 (1993), pp. 1533-1564; G. L. Bundy and F. H. Lincoln, "Synthesis of 17-Phenyl-18,19,20-Trinorprostaglandins: I. The PG_1 Series", Prostaglandins, Vol. 9 No. 1 (1975), pp. 1-4; W. Bartman, G. Beck, U. Lerch, H. Teufel, and B. Scholkens, "Luteolytic Prostaglandins: Synthesis and Biological Activity", Prostaglandins, Vol. 17 No. 2 (1979),

pp. 301-311; C. liljebris, G. Selen, B. Resul, J. Sternschantz, and U. Hacksell, "Derivatives of 17- Phenyl-18,19,20-trinorprostaglandin $F_{2}\alpha$ Isopropyl Ester: Potential Antiglaucoma Agents", Journal of Medicinal Chemistry, Vol. 38 No. 2 (1995), pp. 289-304.

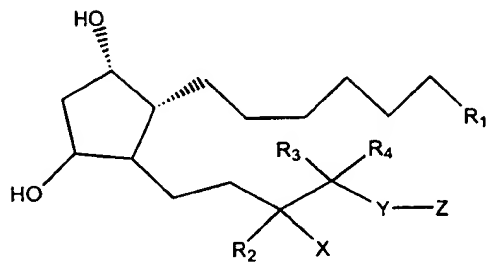
Naturally occurring prostaglandins are known to possess a wide range of pharmacological properties. For example, prostaglandins have been shown to: relax smooth muscle, which results in vasodilatation and bronchodilatation, to inhibit gastric acid secretion, to inhibit platelet aggregation, to reduce intraocular pressure, and to induce labor. Although naturally occurring prostaglandins are characterized by their activity against a particular prostaglandin receptor, they generally are not specific for any one prostaglandin receptor. Therefore, naturally-occurring prostaglandins are known to cause side effects such as inflammation, as well as surface irritation when administered systemically. It is generally believed that the rapid metabolism of the naturally occurring prostaglandins following their release in the body limits some of the effects of the prostaglandin to a local area. This effectively prevents the prostaglandin from stimulating prostaglandin receptors throughout the body and causing the effects seen with the systemic administration of naturally occurring prostaglandins.

Prostaglandins, especially prostaglandins of the E series (PGE), are known to be potent stimulators of bone resorption. $PGF_{2\alpha}$ has also been shown to be a stimulator of bone resorption but not as potent as PGE_2. Also, it has been demonstrated the $PGF_{2\alpha}$ has little effect on bone formation. It has been suggested that some of the effects of $PGF_{2\alpha}$ on bone resorption, formation and cell replication may be mediated by an increase in endogenous PGE_2 production.

In view of both the wide range of pharmacological properties of naturally occurring prostaglandins and of the side effects seen with the systemic administration of these naturally occurring prostaglandins, attempts have been made to prepare analogs to the naturally occurring prostaglandins that are selective for a specific receptor or receptors. A number of such analogs have been disclosed in the art. Though a variety of prostaglandin analogs have been disclosed, there is a continuing need for potent, selective prostaglandin analogs for the treatment of a variety diseases and conditions.

SUMMARY OF THE INVENTION

The invention provides novel PGF analogs. In particular, the present invention relates to compounds having a structure according to the following formula:



wherein R_1, R_2, R_3, R_4, X, Y, and Z are defined below.

This invention also includes optical isomers, diastereomers and enantiomers of the formula above, and pharmaceutically-acceptable salts, biohydrolyzable amides, esters, and imides thereof.

The compounds of the present invention are useful for the treatment of a variety of diseases and conditions, such as bone disorders and glaucoma. Accordingly, the invention further provides pharmaceutical compositions comprising these compounds. The invention still further provides methods of treatment for bone disorders and glaucoma using theses compounds or the compositions containing them.

DETAILED DESCRIPTION OF THE INVENTION

Terms and Definitions

"Acyl' is a group suitable for acylating a nitrogen atom to form an amide or carbamate or an oxygen atom to form an ester group. Preferred acyl groups include benzoyl, acetyl, tert-butyl acetyl, para-phenyl benzoyl, and trifluoroacetyl. More preferred acyl groups include acetyl and benzoyl. The most preferred acyl group is acetyl.

"Alkyl" is a saturated or unsaturated hydrocarbon chain having 1 to 18 carbon atoms, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4 carbon atoms. Alkyl chains may be straight or branched. Preferred branched alkyl have one or two branches, preferably one branch. Preferred alkyl are saturated. Unsaturated alkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated alkyl have one or two double bonds or one triple bond, more preferably one double bond. Alkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred alkyl are unsubstituted. Preferred substituted alkyl are mono-, di-, or trisubstituted. Preferred alkyl substituents include halo, hydroxy, aryl (e.g., phenyl, tolyl, alkyloxphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, and heteroaryl.

"Aromatic ring" is an aromatic hydrocarbon ring system. Aromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic aromatic rings contain from about 5 to about 10 carbon atoms, preferably from 5 to 7 carbon atoms, and most

preferably from 5 to 6 carbon atoms in the ring. Bicyclic aromatic rings contain from 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring. Aromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred aromatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred aromatic rings include naphthyl and phenyl. The most preferred aromatic ring is phenyl.

"Carbocyclic aliphatic ring" is a saturated or unsaturated hydrocarbon ring. Carbocyclic aliphatic rings are not aromatic. Carbocyclic aliphatic rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic carbocyclic aliphatic rings contain from about 4 to about 10 carbon atoms, preferably from 4 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic carbocyclic aliphatic rings contain from 8 to 12 carbon atoms, preferably from 9 to 10 carbon atoms in the ring. Carbocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred carbocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred carbocyclic aliphatic rings include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. More preferred carbocyclic aliphatic rings include cyclohexyl, cycloheptyl, and cyclooctyl. The most preferred carbocyclic aliphatic ring is cycloheptyl.

"Halo" is fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred are chloro and fluoro, especially fluoro.

"Haloalkyl" is a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Preferred haloalkyl are C_1-C_{12}; more preferred are C_1-C_6; more preferred still are C_1-C_3. Preferred halo substituents are fluoro and chloro. The most preferred haloalkyl is trifluoromethyl.

"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 1 to 18 member atoms (carbon and heteroatoms) in the chain, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more double bonds and/or one or more triple bonds. Preferred unsaturated heteroalkyl have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred heteroalkyl are unsubstituted. Preferred heteroalkyl substituents include halo,

hydroxy, aryl (e.g., phenyl, tolyl, alkyloxphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl. For example, alkyl substituted with the following substituents are heteroalkyl: alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionyloxy, benzoyloxy, acetoxy), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio, chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkyloxycarbonylphenylthio), amino (e.g., amino, mono- and di- C_1-C_3 alkanylamino, methylphenylamino, methylbenzylamino, C_1-C_3 alkanylamido, carbamamido, ureido, guanidino).

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms.

"Heterocyclic aliphatic ring" is a saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring, wherein no two heteroatoms are adjacent in the ring and no carbon in the ring that has a heteroatom attached to it also has a hydroxyl, amino, or thiol group attached to it. Heterocyclic aliphatic rings are not aromatic. Heterocyclic aliphatic rings are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocyclic aliphatic rings contain from about 4 to about 10 member atoms (carbon and heteroatoms), preferably from 4 to 7, and most preferably from 5 to 6 in the ring. Bicyclic heterocyclic aliphatic rings contain from 8 to 12 member atoms, preferably 9 or 10 in the ring. Heterocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred heterocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred heterocyclic aliphatic rings include piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperdyl.

"Heteroaromatic ring" is an aromatic ring system containing carbon and from 1 to about 4 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10 member atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 in the ring. Bicyclic heteroaromatic rings contain from 8 to 12 member atoms, preferably 9 or 10 in the ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred heteroaromatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo, haloalkyl, and phenyl. Preferred heteroaromatic rings include thienyl, thiazolo, purinyl, pyrimidyl, pyridyl, and

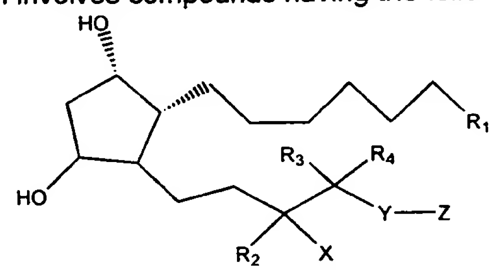
furanyl. More preferred heteroaromatic rings include thienyl, furanyl, and pyridyl. The most preferred heteroaromatic ring is thienyl.

"Lower alkyl" is an alkyl chain radical comprised of 1 to 6, preferably 1 to 4 carbon atoms.

"Phenyl" is a monocyclic aromatic ring which may or may not be substituted with from about 1 to about 4 substituents. The substituents may be substituted at the *ortho*, *meta* or *para* position on the phenyl ring, or any combination thereof. Preferred phenyl substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents on the phenyl ring include halo and haloalkyl. The most preferred substituent is halo. The preferred substitution pattern on the phenyl ring is *ortho* or *meta*. The most preferred substitution pattern on the phenyl ring is *ortho*.

Compounds

The subject invention involves compounds having the following structure:



In the above structure, R_1 is CO_2H, C(O)NHOH, CO_2R_5, CH_2OH, $S(O)_2R_5$, $C(O)NHR_5$, $C(O)NHS(O)_2R_5$, or tetrazole; wherein R_5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred R_5 is CH_3, C_2H_5, C_3H_7. Preferred R_1 is CO_2H, C(O)NHOH, CO_2CH_3, $CO_2C_2H_5$, $CO_2C_3H_7$, $CO_2C_4H_9$, $CO_2C_3H_7O_2$, and $C(O)NHS(O)_2R_5$. More preferred R_1 is CO_2H, C(O)NHOH, CO_2CH_3, and $CO_2C_3H_5$. Most preferred R_1 is CO_2H and CO_2CH_3.

In the above structure, R_2 is H or lower alkyl. Preferred R_2 is H and CH_3. Most preferred R_2 is H.

In the above structure, X is NR_6R_7, OR_8, SR_9, $S(O)R_9$, or $S(O)_2R_9$; wherein R_6,R_7, and R_8 are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaromatic ring; and wherein R_9 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred R_6 and R_7 are H, CH_3 and C_2H_5. Preferred R_8 is H, CH_3, C_2H_5, and C_3H_7. Preferred R_9 is CH_3 and C_2H_5. Preferred X is NR_6R_7 and OR_8. Most preferred X is OH.

In the above structure, R_3 and R_4 are independently selected from the group consisting of H, CH_3, and C_2H_5. Preferred R_3 and R_4 are H.

In the above structure, Y is NR_{10}, S, S(O), or $S(O)_2$; wherein R_{10} is H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred R_{10} is H and CH_3. Preferred Y is NH and S.

In the above structure, Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring. Preferred Z is monocyclic carbocyclic aliphatic ring, monocyclic heterocyclic aliphatic ring, monocyclic aromatic ring, and monocyclic heteroaromatic ring. More preferred Z is monocyclic aromatic ring or monocyclic heteroaromatic ring. The most preferred Z is thienyl or phenyl.

The invention also includes optical isomers, diastereomers and enantiomers of the above structure. Thus, at all stereocenters where stereochemistry is not defined (C_{11}, C_{12}, C_{15}, and C_{16}), both epimers are envisioned. Preferred stereochemistry at all such stereocenters of the compounds of the invention mimic that of naturally occurring PGF_{2a}.

It has been discovered that the novel PGF analogs of the subject invention are useful for treating bone disorders, especially those that require a significant increase in bone mass, bone volume, or bone strength. Surprisingly, the compounds of the subject invention have been found to provide the following advantages over known bone disorder therapies: (1) An increase trabecular number through formation of new trabeculae; (2) An increase in bone mass and bone volume while maintaining a more normal bone turnover rate; and (3) An increase in bone formation at the endosteal surface without increasing cortical porosity.

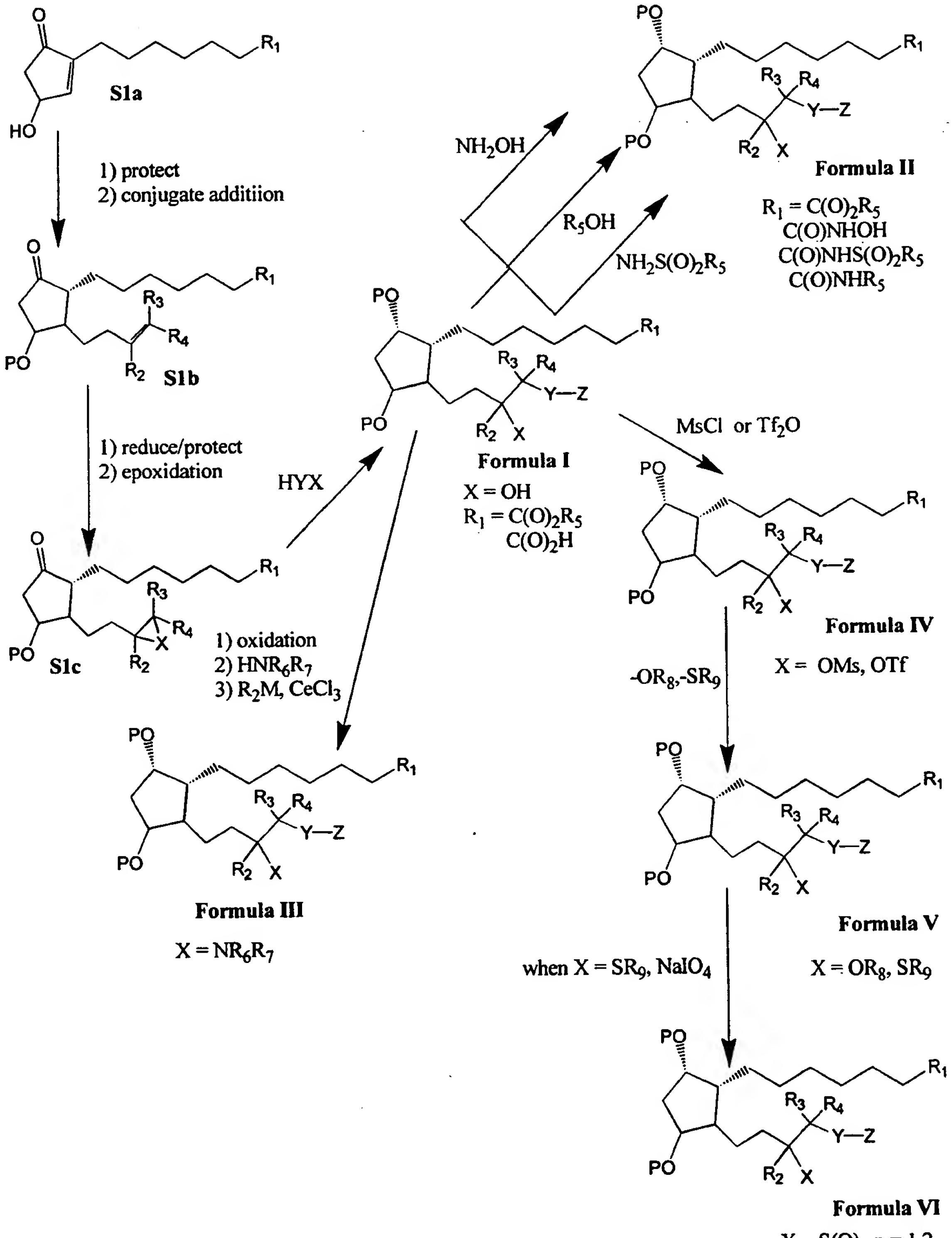
In order to determine and assess pharmacological activity, testing of the subject compounds in animals is carried out using various assays known to those skilled in the art. For example, the bone activity of the subject compounds can be conveniently demonstrated using an assay designed to test the ability of the subject compounds to increase bone volume, mass, or density. An example of such assays is the ovariectomized rat assay.

In the ovariectomized rat assay, six-month old rats are ovariectomized, aged 2 months, and then dosed once a day subcutaneously with a test compound. Upon completion of the study, bone mass and/or density can be measured by dual energy x-ray absorptometry (DXA) or peripheral quantitative computed tomography (pQCT), or micro computed tomography (mCT). Alternatively, static and dynamic histomorphometry can be used to measure the increase in bone volume or formation.

Pharmacological activity for glaucoma can be demonstrated using assays designed to test the ability of the subject compounds to decrease intraocular pressure. Examples of such assays are described in the following reference, incorporated herein: C. liljebris, G. Selen, B. Resul, J. Sternschantz, and U. Hacksell, "Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin $F_{2}\alpha$ Isopropyl Ester: Potential Antiglaucoma Agents", Journal of Medicinal Chemistry, Vol. 38 No. 2 (1995), pp. 289-304.

Compounds useful in the subject invention can be made using conventional organic syntheses. A particularly preferred synthesis is the following general reaction scheme:

Scheme 1



In **Scheme 1**, R_1, R_2, R_3, R_4, X, Y, and Z are as defined above. The Methyl 7[3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl] heptanoate (**S1a**) depicted as starting material

for **Scheme 1** is commercially available (such as from Sumitomo Chemical or Cayman Chemical).

In the above **Scheme 1**, Methyl 7-[3-(R)-hydroxy-5-oxo-1-cyclopent-1-yl] heptanoate (**S1a**) is reacted with a silylating agent and base in a solvent that will allow the silylation to proceed. Preferred silylating agents include tert-butyldimethylsilyl chloride and tert-butyldimethylsilyl trifluoromethanesulphonate. The most preferred silylating agent is tert-butyldimethylsilyl trifluoromethanesulphonate. Preferred bases include triethylamine, trimethylamine, and 2,6-lutidine. More preferred bases include triethylamine and 2,6-lutidine. The most preferred base is 2,6-lutidine. Preferred solvents include halocarbon solvents with dichloromethane being the most preferred solvent. The reaction is allowed to proceed at a temperature preferably between -100°C and 100°C, more preferably between -80°C and 80°C, and most preferably between -70°C and 23°C.

The resulting silylated compound is isolated by methods known to those of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, the silyl ether is purified after isolation by distillation under vacuum.

The silylated compound is then reacted with the cuprate generated via Grignard formation of the appropriate alkenyl bromide as disclosed, for example, in the following references: H.O. House et. al., "The Chemistry of Carbanions: A Convenient Precursor for the Generation of Lithium Organocuprates", J. Org. Chem. Vol. 40 (1975) pp. 1460-69 ; and P. Knochel et. al.,'"Zinc and Copper Carbenoids as Efficient and Selective a'/d' Multicoupling Reagents", J. Amer.Chem. Soc. Vol. 111 (1989) p. 6474-76. Preferred alkenyl bromides include 4-bromo-1-butene, 4-bromo-1-butyne, 4-bromo-2-methyl-1-butene, and 4-bromo-2-ethyl-1-butene. The most preferred alkenyl bromide is 4-bromo-1-butene. Preferred solvents include ethereal solvents, of which diethyl ether and tetrahydrofuran are preferred. The most preferred solvent is tetrahydrofuran. The Grignard reagent is allowed to form at a temperature between 100°C and 23°C, more preferably between 85°C and 30°C, and most preferably between 75°C and 65°C. The reaction time is preferably between 1 hour and 6 hours, with a more preferred reaction time being between 2 hours and 5 hours, and the most preferred reaction time being between 3 hours and 4 hours.

Once the Grignard reagent is formed, the cuprate is generated from the alkenyl magnesium species. The temperature range for cuprate formation is between -100°C and 0°C. The preferred temperature range is between -80°C and -20°C. The more preferred temperature range is between -75°C and -50°C. The preferred reaction time

is between 30 minutes and 6 hours. The more preferred reaction time is between 45 minutes and 3 hours. The most preferred reaction time is between 1 hours and 1.5 hours.

The compound depicted as **S1b** is isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, **S1b** is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 10% EtOAc/hexanes as the eluent.

S1b is then reacted with a hydride reducing agent and a polar, protic solvent to give the C_9 alcohol. Preferred reducing agents include lithium aluminum hydride, sodium borohydride, and L-selectride. More preferred reducing agents include sodium borohydride, and L-selectride. The most preferred reducing agent is sodium borohydride. Preferred solvents include methanol, ethanol, and butanol. The most preferred solvent is methanol. The reduction is carried out at a temperature between -100^{o}C and 23^{o}C. The preferred temperature range is between -60^{o}C and 0^{o}C. The most preferred temperature range is between -45^{o}C and -20^{o}C.

The resulting alcohol of **S1b** is isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, the alcohol is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

The alcohol can be protected as described previously herein. The protected or unprotected alcohol is then treated with meta-chloroperbenzoic acid in a halocarbon solvent to provide the novel epoxide intermediate depicted as **S1c**. Preferred halocarbon solvents include dichloromethane, dichloroethane, and chloroform. More preferred halocarbon solvents are dichloromethane and dichloroethane. The most preferred halocarbon solvent is dichloromethane.

The compound depicted as **S1c** is isolated by methods known to one of ordinary skill in the art. Such methods include, but are not limited to, extraction, solvent evaporation, distillation, and crystallization. Preferably, **S1b** is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 20% EtOAc/hexanes as the eluent.

The intermediate epoxide depicted as **S1c** can be reacted with a variety of oxygen, sulfur and nitrogen containing nucleophiles as disclosed, for example, in J.G. Smith, "Synthetically Useful Reactants of Epoxides", Synthesis (1984) p. 629-656, to

provide the C_{11}-protected 13,14-dihydro-15-substituted-16-tetranor Prostaglandin $F_{1\alpha}$ derivatives of **Formula I**.

With sulfur nucleophiles, the reaction is carried out preferably at between 150°C and 0°C, more preferably between 120°C and 20°C, and most preferably between 80°C and 50°C. Preferred bases for the reaction include triethylamine, N,N diisopropylethylamine, and trimethylamine. The most preferred base is triethylamine. Preferred solvents for the reaction are aromatic hydrocarbon solvents. Preferred solvents include xylenes, toluene, and benzene. The most preferred solvent is benzene. With nitrogen and oxygen nucleophiles, preferred solvents include ethereal solvents and polar, protic solvents. More preferred ethereal solvents include diethyl ether, dibutyl ether and tetrahydrofuran. The most preferred ethereal solvent is tetrahydrofuran. More preferred polar, protic solvents include ethyl alcohol, methyl alcohol, and tert-butyl alcohol. The most preferred polar, protic solvent is ethyl alcohol.

The ring-opening process with nitrogen and oxygen nucleophiles can be catalyzed with Lewis acids. Preferred Lewis acids include magnesium perchlorate, trimethylsilyl trifluoromethanesulphonate, and trimethylaluminum. The most preferred Lewis acid is magnesium perchlorate. The reaction is carried out at a temperature between 150°C and 23°C, preferably between 125°C and 40°C, and more preferably between 100°C and 75°C.

The resulting compounds can be isolated, but are generally deprotected using techniques known to one of ordinary skill in the art, and isolated as the final 13,14-dihydro-15-substituted-16-tetranor prostaglandin $F_{1\alpha}$ derivative. Compounds depicted by **Formula I** are exemplified in Examples 2-28.

Compounds depicted by **Formula II** can be made directly from those described in **Formula I** by methods known to one of ordinary skill in the art. For example, the condensation of methyl esters of **Formula I** with amines or hydroxylamine provides compounds depicted by **Formula II**. Compounds depicted by **Formula II** are exemplified in Examples 29-32.

Compounds depicted by **Formula III** can be made directly from those described in **Formula I** by methods known to one of ordinary skill in the art. The appropriately protected derivative from **Formula I** is oxidized to the ketone following the process described in the following references: A. McKillop and D.W. Young, "Organic Synthesis Using Supported Reagents - Part 1", Synthesis (1979) p. 401-22; G. Piancatelli et al., "Pyridium Chlorochromate: A Versatile Oxidation Organic Synthesis", Synthesis (1982) p. 245-58; E.J. Corey and J.W. Suggs, "Pyridinium Chlorochromate: An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds", Tetrahedron

Lett. Vol. 31 (1975) p. 2647-50; and references cited therein. The ketone is then condensed with N-methylamine to give the imine. Addition of the methylcerium nucleophile (~1.5 equiv.), as described for example in T. Imamoto, et al., "Carbon-Carbon Bond Forming Reactions Using Cerium Metal or Organcerium (III) Reagents", J. Org. Chem. Vol. 49 (1984) p. 3904-12; T. Imamoto, et al., "Reactions of Carbonyl Compounds with Grignard Reagents in the Presence of Cerium Chloride", J. Am. Chem. Soc. Vol. 111 (1989) p. 4392-98; and references cited therein, gives the aminomethyl derivative of **Formula III.** Compounds depicted by **Formula III** are exemplified in Examples 39- 42.

Compounds depicted by **Formula IV** and **Formula V** can be made from compounds described in **Formula I** by activation and subsequent nucleophilic displacement of the appropriately functionalized hydroxyl group. Transformations of this type are described in the following references: E.J. Corey et al., "Simple Stereospecific Routes to 9-epi-Prostaglandin $F_{2}\alpha$", J.C.S. Chem. Comm. (1975) p. 658-9; E.J. Corey et al., "Superoxide ion as a Synthetically Useful Oxygen Nucleophile", Tetrahedron Lett. (1975) p. 3183-6; E.J. Corey et al., "Total Synthesis of 5-desoxy Leukotriene D. A New and Useful Equivalent of the 4-Formyl-Trans,Trans-1,3-Butadienyl Anion", Tetrahedron Lett. Vol. 23 (1982) p. 3463-66; and references cited therein. Compounds depicted by **Formula V** are exemplified in Examples 33-36.

Compounds depicted by **Formula VI** can be made from those described in **Formula V** (where X is SR_9) by selective oxidation procedures as described, for example, in the following references: E.J. Corey et al., "Pathways for Migration and Cleavage of the S-Peptide Unit of the Leukotrienes", Tetrahedron Lett. Vol. 23 (1982) p. 3467-70; Prostaglandins Vol. 24 (1982) p. 801; Y. Girard et al., "Synthesis of the Sulfones of Leukotrienes C_4, D_4, and E_4", Tetrahedron Lett. Vol. 23 (1982) p. 1023-26; and references cited therein. Compounds depicted by **Formula VI** are exemplified in Examples 37-38.

The following non-limiting examples illustrate the compounds, compositions, and uses of the present invention.

Examples

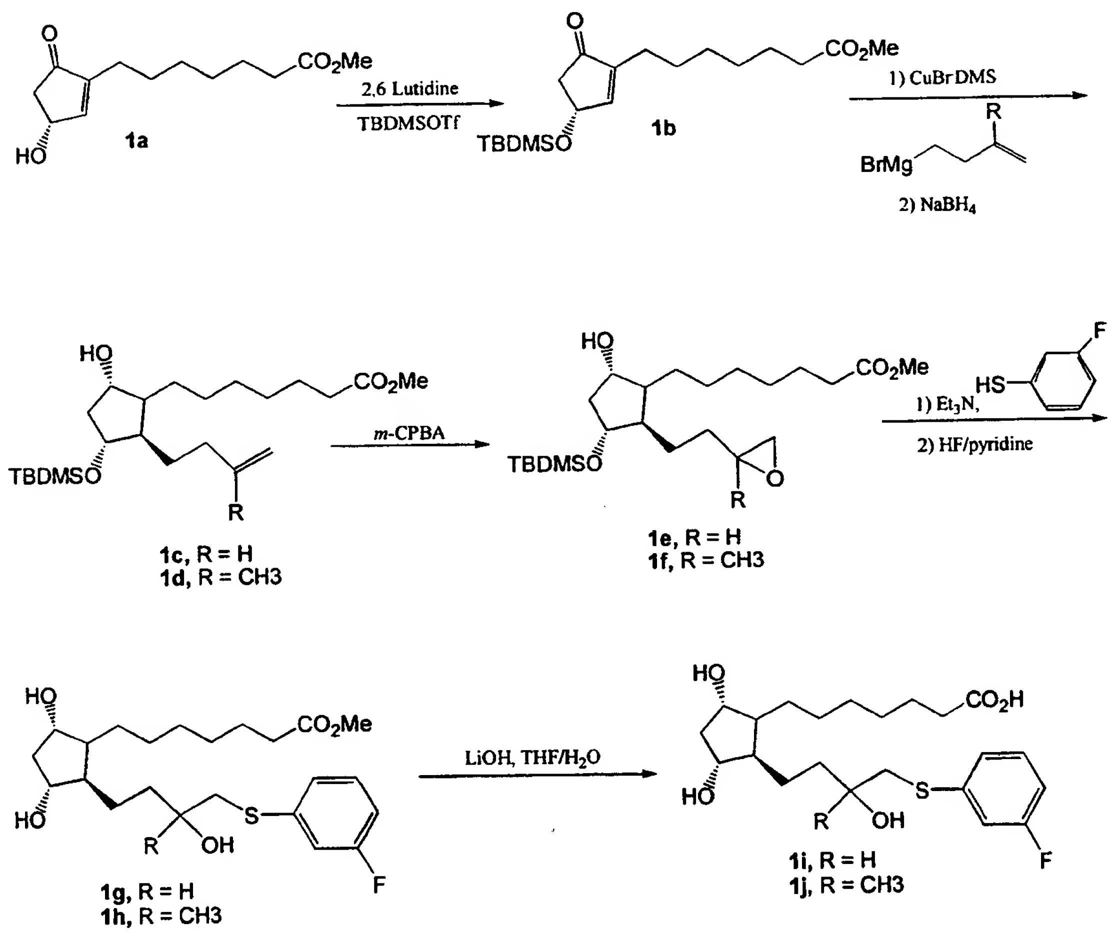
Compounds are analyzed using ^{1}H and ^{13}C NMR, Elemental analysis, mass spectra, high resolution mass spectra and/or IR spectra as appropriate.

Typically, inert solvents are used, preferably in dried form. For example, tetrahydrofuran (THF) is distilled from sodium and benzophenone, diisopropylamine is distilled from calcium hydride and all other solvents are purchased as the appropriate grade. Chromatography is performed on silica gel (70-230 mesh; Aldrich) or (230-400

mesh; Merck) as appropriate. Thin layer chromatography analysis is performed on glass mounted silica gel plates (200-300 mesh; Baker) and visualized using UV, 5% phosphomolybdic acid in EtOH, or ammonium molybdate/cerric sulfate in 10% aqueous H_2SO_4.

EXAMPLE 1

Preparation of 13,14-dihydro-16-(3-fluorophenylthio) tetranor prostaglandin $F_{1\alpha}$ (1i), and 13,14-dihydro-15-methyl-16-(3-fluorophenylthio) tetranor prostaglandin $F_{1\alpha}$ (1j) :



a. **Methyl 7-(2-oxo-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclopent-1-enyl) heptanoate 1b:** To a solution of Methyl-7-[3-(R)-hydroxy-5-oxo-1-cyclopenten-1-yl] heptanoate **1a** (1 equiv.) in CH_2Cl_2 at -78°C is added 2,6 Lutidine (1.3 equiv.) dropwise over 15 minutes. The solution is kept at -78°C, and TBDMS Triflate (1.2 equiv.) in CH_2Cl_2 is added dropwise over 15 minutes. The reaction is warmed gradually to room

temperature and stirred at room temperature for 15 hours. Aqueous 10% HCl is added and the layers are separated. The water layer is extracted with CH_2Cl_2 and the organic layers are combined. The organic layer is washed with brine, dried (Na_2SO_4) and concentrated. The residue is distilled under vacuum (10 mm Hg) to provide the silyl ether **1b** as a yellow liquid.

b. Methyl 7-(5-but-3-enyl-2-hydroxy-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclopentyl) heptanoate 1c, 1d: To a slurry of Mg^0 powder (2 equiv.) in THF at room temperature is added one crystal of I_2 and 1-bromobutene (2 equiv.) dropwise over 10 minutes. The reaction proceeds to exotherm as the addition continues. After the addition is complete, the reaction is refluxed for 3 hours and cooled to room temperature. The Grignard is diluted with THF and added via cannula to a 3-necked flask equipped with mechanical stirring and charged with CuBr.DMS (2 equiv.) in a 1:1 solution of THF/DMS at -78°C. After the addition of the Grignard (~20 min), the reaction is stirred for 1 hour at -78°C. The color of the reaction is dark red at this point. A solution of the ketone **1b** (1 equiv.) in THF is then added dropwise over 25 minutes. The reaction is stirred at -78°C for 15 minutes, then allowed to warm slowly to room temperature over 2 hours. The reaction is quenched with aqueous NH_4Cl and the excess DMS is allowed to evaporate overnight. The reaction is partitioned between brine/CH_2Cl_2 and the layers are separated. The aqueous layer is back-extracted with CH_2Cl_2 and the organic layers are combined and dried (Na_2SO_4). The solvent is removed in vacuo and the residue is chromatographed on SiO_2 (10 % hexane/EtOAc) to give the ketone precursor to **1c** as a clear oil. The ketone precursor to **1d** is prepared in substantially the same manner.

The ketone precursor to **1c** (1 equiv.) is dissolved in MeOH and cooled to -40°C. Sodium borohydride (0.9 equiv.) is added portionwise over 10 minutes. After the addition is complete, the reaction is stirred for 13 hours at -40°C and then for 12 hours at -78°C. The reaction is quenched with water, partitioned between brine and CH_2Cl_2, and the layers separated. The aqueous layer is back-extracted with CH_2Cl_2 and the organic layers are combined and dried (Na_2SO_4). The solvent is removed in vacuo and the residue chromatographed on SiO_2 (30 % EtOAc/hexanes) to give the alcohol **1c** as a colorless oil. Alcohol **1d** is prepared in substantially the same manner.

c. Methyl 7-(2-hydroxy-5-(2-(2-oxiranyl)ethyl-4-(1,1,2,2-tetramethyl-1-silapropoxy)cyclopentyl) heptanoate 1e, 1f: The alcohol **1c** (1 equiv.) is dissolved in CH_2Cl_2 and cooled to 0°C. Sodium bicarbonate is added, followed by m-CPBA (57%-85% purity) (3 equiv.) portionwise over 15 minutes. After the addition is complete, the reaction is stirred for 20 hours at room temperature. The reaction is poured into water,

partitioned between brine and CH_2Cl_2, and the layers are separated. The aqueous layer is back-extracted with CH_2Cl_2 and the organic layers are combined and dried (Na_2SO_4). The solvent is removed in vacuo and the residue is chromatographed on SiO_2 (20% EtOAc/hexanes) to give the epoxide diasteriomers **1e** as a colorless oil. Compound **1f** is synthesized in substantially the same manner.

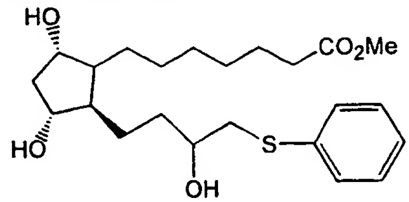
d. 13,14-dihydro-16-(3-fluorophenylthio) tetranor prostaglandin $F_{1\alpha}$ (1g), and 13,14-dihydro-15-methyl-16-(3-fluorophenylthio) tetranor prostaglandin $F_{1\alpha}$ (1h) methyl esters: In a 5 mL round-bottomed flask, epoxide **1e** (1 equiv.) and 100 uL of dry benzene are added. The flask is cooled to 0°C, then is treated with 60 uL of 3-fluoro thiophenol (1.2 eq) and 78 uL of triethyl amine (1.2 eq) as disclosed in J.G. Smith, "Synthetically Useful Reactants of Epoxides", Synthesis (1984) p. 629-656, and references cited therein. The ice bath is removed and the reaction is stirred at room temperature under nitrogen overnight. TLC is used to monitor the reaction. Excess thiophenol is added if necessary. The reaction is quenched with brine and is extracted with methylene chloride. The organic layer is washed three times with 1N HCl, brine, dried over sodium sulfate, and concentrated. Without further purification to this crude reaction mixture, 3 mL of CH_3CN and 0.1 mL of HF/Pyridine (0.1 mmol) are added while the flask is kept at 0°C. After 3 hours at 0°C, the reaction is quenched with saturated NaCl. The aqueous layer is extracted three times with CH_2Cl_2. The organic layers are combined and washed three time with 1N HCl, brine, and dried (Na_2SO_4). After column chromatography, (7:3, Hexane: Ethyl Acetate) the clear oil **1g** is obtained. The ester **1h** is prepared in substantially the same manner.

e. 13,14-dihydro-16-(3-fluorophenylthio) tetranor prostaglandin $F_{1\alpha}$ (1i), and 13,14-dihydro-15-methyl-16-(3-fluorophenylthio) tetranor prostaglandin $F_{1\alpha}$ (1j): To a 5 ml round-bottomed flask, 50 mg (0.12 mmol) of 13,14-dihydro-16-(3-fluorophenylthio) tetranor Prostaglandin $F_{1\alpha}$ methyl ester **1g** and 4 mL of THF water solution (3:1, THF:H_2O) are added, and the flask is cooled at 0°C. An excess amount (2.5 equiv.) of lithium hydroxide is added, the ice bath is removed, and the reaction is stirred at room temperature overnight. Methylene chloride and saturated citric acid are added to the reaction mixture, the aqueous layer is washed 3 times with methylene chloride, the organic layers are combined and washed with brine, dried (Na_2SO_4), concentrated in vacuo, and the residue is chromatographed (methylene chloride, methanol, acetic acid, 9.6, 0.4, 0.015), to provide 30 mg of the clear oil **1i**. The acid **1j** is prepared in substantially the same manner.

Utilizing substantially the method of Example 1 (and using the appropriate thiophenol), the following subject compounds of Examples 2-23 are obtained.

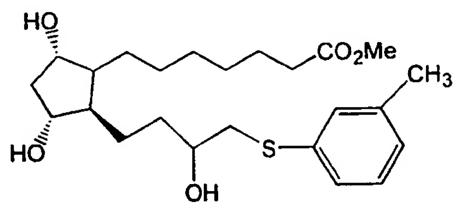
Example 2

13,14-dihydro-16-(phenylthio) tetranor Prostaglandin $F_{1\alpha}$ methyl ester



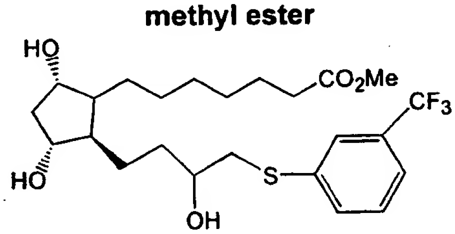
Example 3

13,14-dihydro-16-(3-methylphenylthio) tetranor Prostaglandin $F_{1\alpha}$ methyl ester



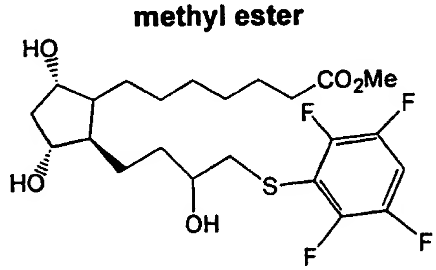
Example 4

13,14-dihydro-16-(3-trifluoromethylphenylthio) tetranor Prostaglandin $F_{1\alpha}$ methyl ester



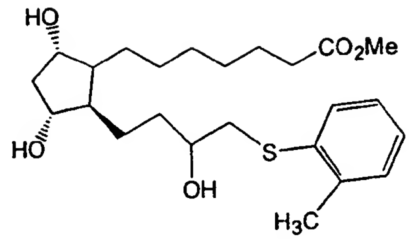
Example 5

13,14-dihydro-16-(2,3,5,6-tetrafluorophenylthio) tetranor Prostaglandin $F_{1\alpha}$ methyl ester



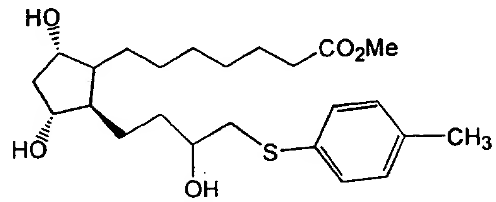
Example 6

13,14-dihydro-16-(2-methylphenylthio) tetranor Prostaglandin $F_{1\alpha}$ methyl ester



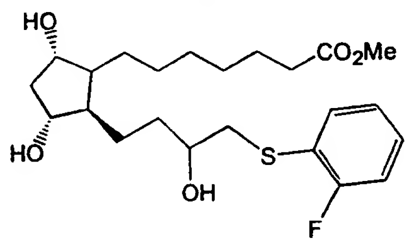
Example 7

13,14-dihydro-16-(4-methylphenylthio) tetranor Prostaglandin F1α methyl ester



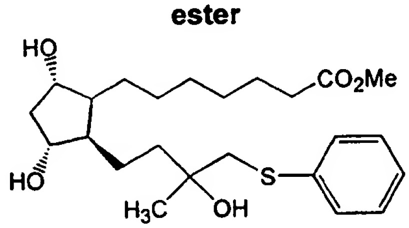
Example 8

13,14-dihydro-16-(2-fluorophenylthio) tetranor Prostaglandin F1α methyl ester



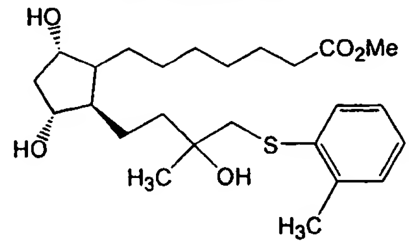
Example 9

13,14-dihydro-15-methyl-16-(phenylthio) tetranor Prostaglandin F1α methyl ester



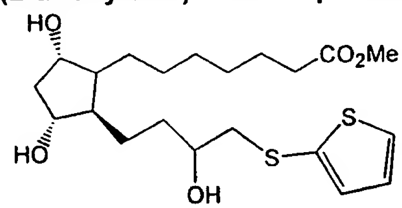
Example 10

13,14-dihydro-15-methyl-16-(2-methylphenylthio) tetranor Prostaglandin F1 α methyl ester



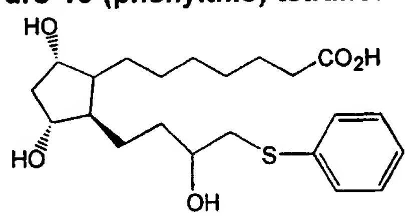
Example 11

13,14-dihydro-16-(2-thienylthio) tetranor prostaglandin F1α methyl ester



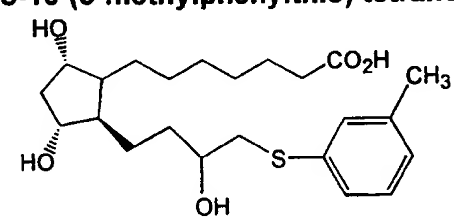
Example 12

13,14-dihydro-16-(phenylthio) tetranor Prostaglandin F1α



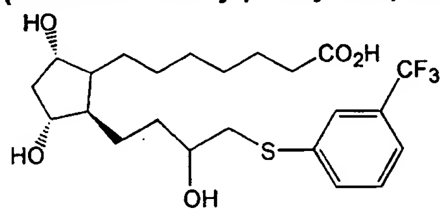
Example 13

13,14-dihydro-16-(3-methylphenylthio) tetranor Prostaglandin F1α



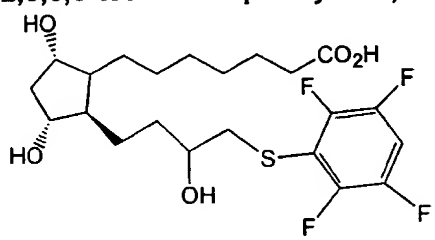
Example 14

13,14-dihydro-16-(3-trifluoromethylphenylthio) tetranor Prostaglandin F1α



Example 15

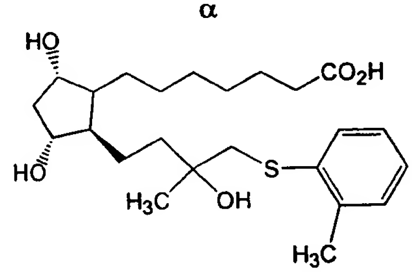
13,14-dihydro-16-(2,3,5,6-tetrafluorophenylthio) tetranor Prostaglandin F1α



Example 16

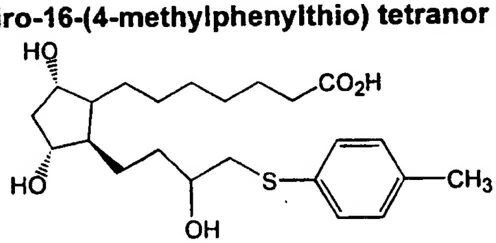
13,14-dihydro-15-methyl-16-(2-methylphenylthio) tetranor Prostaglandin F1

α



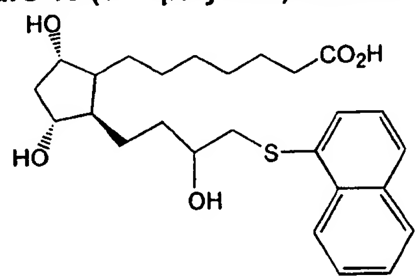
Example 17

13,14-dihydro-16-(4-methylphenylthio) tetranor Prostaglandin F1α



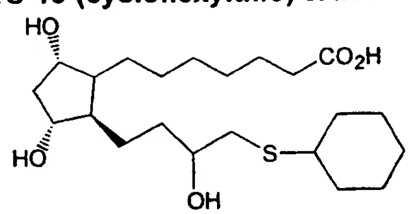
Example 18

13,14-dihydro-16-(1-napthylthio) tetranor Prostaglandin F1α



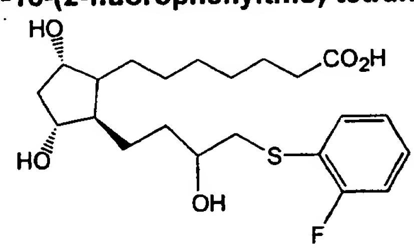
Example 19

13,14-dihydro-16-(cyclohexylthio) tetranor Prostaglandin F1α



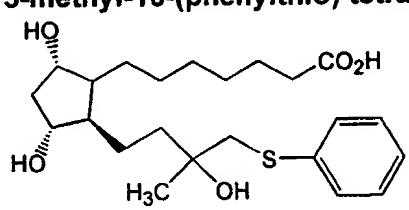
Example 20

13,14-dihydro-16-(2-fluorophenylthio) tetranor Prostaglandin F1α



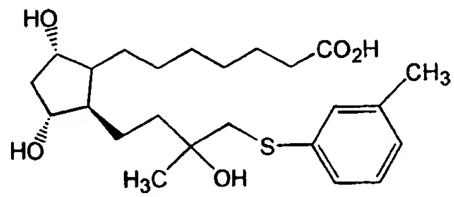
Example 21

13,14-dihydro-15-methyl-16-(phenylthio) tetranor Prostaglandin F1α



Example 22

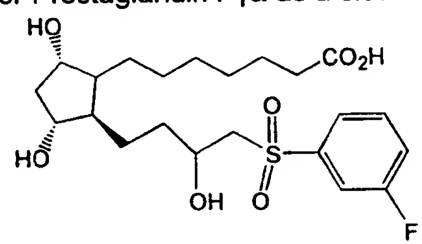
13,14-dihydro-15-methyl-16-(3-methylphenylthio) tetranor Prostaglandin F1 α



Example 23

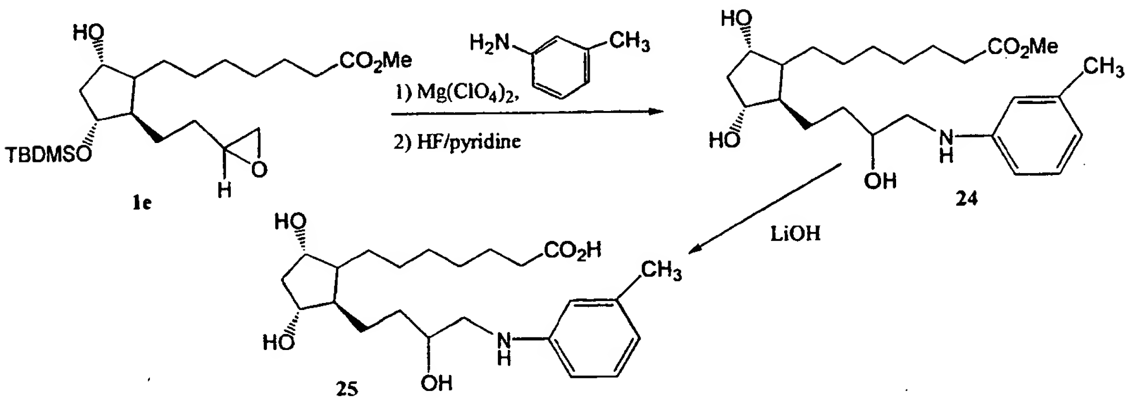
13,14-dihydro-16-(3-fluorophenylsulfonyl) tetranor Prostaglandin F1α:

To a solution of 13,14-dihydro-16-(3-fluorophenylthio) tetranor Prostaglandin F1 α (1 equiv.) in $CHCl_3$ at -78°C is added peracetic acid (2 equiv.) dropwise. The solution is kept at -78°C for 1 hour, then it is allowed to warm to 0°C and is kept at 0°C for 1 hour. Saturated NaCl is added and the layers are separated. The water layer is extracted with CH_2Cl_2 and the organic layers are combined. The organic layer is washed with brine, dried (Na_2SO_4) and concentrated. The residue is chromatographed on SiO_2 (96 CH_2Cl_2, 4 MeOH, 0.1 Acetic acid) to give 13,14-dihydro-16-(3-fluorophenylsulfonyl) tetranor Prostaglandin F1α as a clear oil.



Example 24

Preparation of 13,14-dihydro-16-(3-methylphenylamino) tetranor prostaglandin F_1 α methyl ester:



To a 10 mL round-bottomed flask, epoxide **1e** (1.26 mmol), m-Toludine (1.5 equiv.), 10 mg of magnesium perchlorate and 2 mL THF are added, after which the reaction is refluxed under nitrogen overnight. The flask is cooled to room temperature and the solvent removed in vacuo. Without further purification of this crude reaction mixture, 3 mL of CH_3CN and 0.5 mL of HF/Pyridine (0.5mmol, 0.6 equiv.) are added while the flask is kept at 0°C. After 5 hours at 0°C, the reaction is quenched with saturated NaCl. The aqueous layer is extracted three times with CH_2Cl_2. The organic layers are combined and washed three time with saturated $NaHCO_3$, brine, and dried (Na_2SO_4). After column chromatography (95% CH_2Cl_2, 5% MeOH) 13,14-dihydro-16-(3-methylphenylamino) tetranor prostaglandin $F_{1\alpha}$ methyl ester is obtained as a clear oil.

Example 25

Preparation of 13,14-dihydro-16-(3-methylphenylamino) tetranor prostaglandin F_1 α:

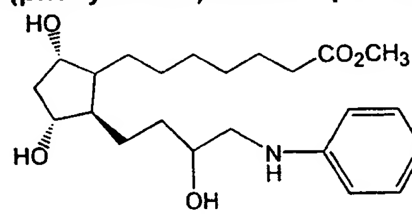
To a 5 ml round-bottomed flask, 13,14-dihydro-16-(3-methylphenylamino) tetranor Prostaglandin $F_{1\alpha}$ methyl ester (0.15 mmol) and 4 mL of THF water solution (3:1, THF:H_2O) are added. The flask is cooled to 0°C, and excess an amount of lithium hydroxide (2.5 equiv.) is added. The ice bath is removed, and the reaction is stirred at room temperature overnight. Methylene chloride and saturated citric acid are added to the reaction mixture, and the aqueous layer is washed 3 times with methylene chloride. The organic layers are combined and washed with brine, dried (Na_2SO_4), concentrated, and chromatographed (methylene chloride, methanol, acetic acid, 9.6,

0.4, 0.015), to provide 13,14-dihydro-16-(3-methylphenylamino) tetranor prostaglandin $F_{1}\alpha$ as a clear oil.

Utilizing substantially the method of Examples 24 and 25 (and using the appropriate aniline), the following subject compounds of Examples 26-28 are obtained.

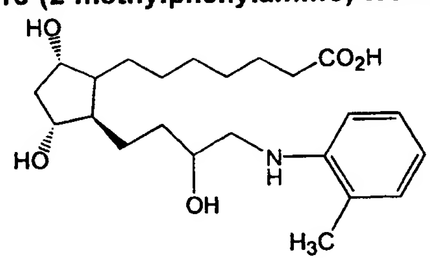
Example 26

13,14-dihydro-16-(phenylamino) tetranor prostaglandin $F_{1}\alpha$ methyl ester



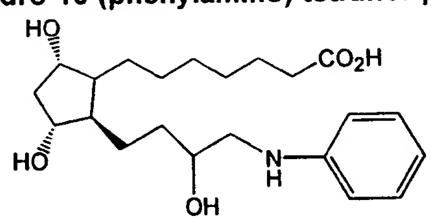
Example 27

13,14-dihydro-16-(2-methylphenylamino) tetranor prostaglandin $F_{1}\alpha$



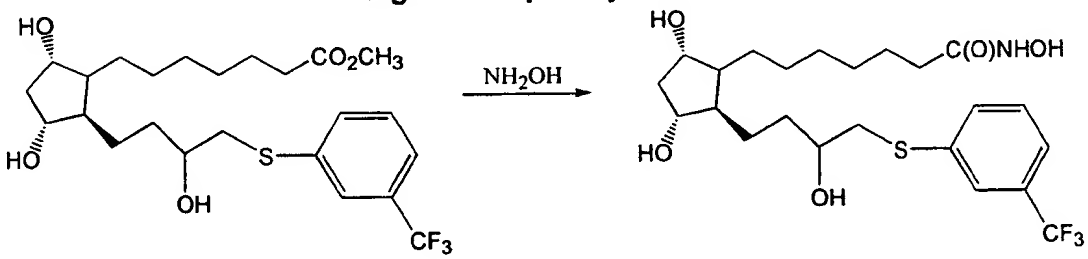
Example 28

13,14-dihydro-16-(phenylamino) tetranor prostaglandin $F_{1}\alpha$



Example 29

Preparation of 13,14-dihydro-16-(3-trifluoromethylphenylthio) tetranor Prostaglandin $F_{1\alpha}$ 1-hydroxamic acid:

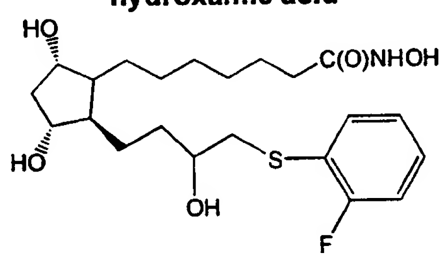


In a flame-dried 25 mL round-bottomed flask equipped with a magnetic stir bar is placed 13,14-dihydro-16-(3-trifluoromethyphenylthio) tetranor Prostaglandin $F_{1\alpha}$ methyl ester (**Example 4**) (1.0 equiv.) in methanol. To this solution is added hydroxylamine in methanol (1.25 equiv.). The solution stirred for 18 hours. The solution is then treated with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer is washed with brine, dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. The residue is purified by chromatography to give 13,14-dihydro-16-(3-trifluoromethylphenylthio) tetranor Prostaglandin $F_{1\alpha}$ 1-hydroxamic acid.

Utilizing substantially the method of Example 29 (using the appropriate hydroxylamine or sulfonamide), the following subject compounds of Examples 30-32 are obtained.

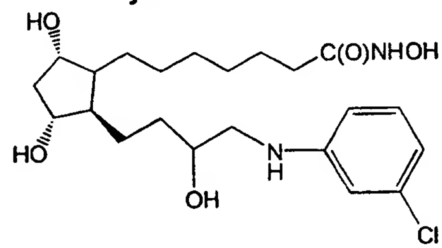
Example 30

13,14-dihydro-16-(2-fluorophenylthio) tetranor Prostaglandin $F_{1\alpha}$ 1-hydroxamic acid



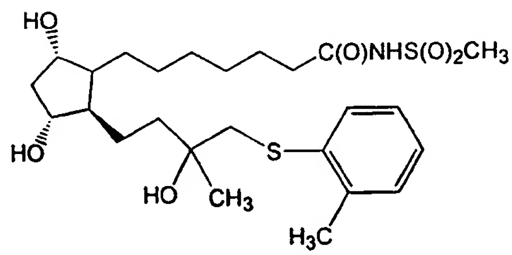
Example 31

13,14-dihydro-16-(3-chlorophenylamino) tetranor Prostaglandin F1α 1-hydroxamic acid



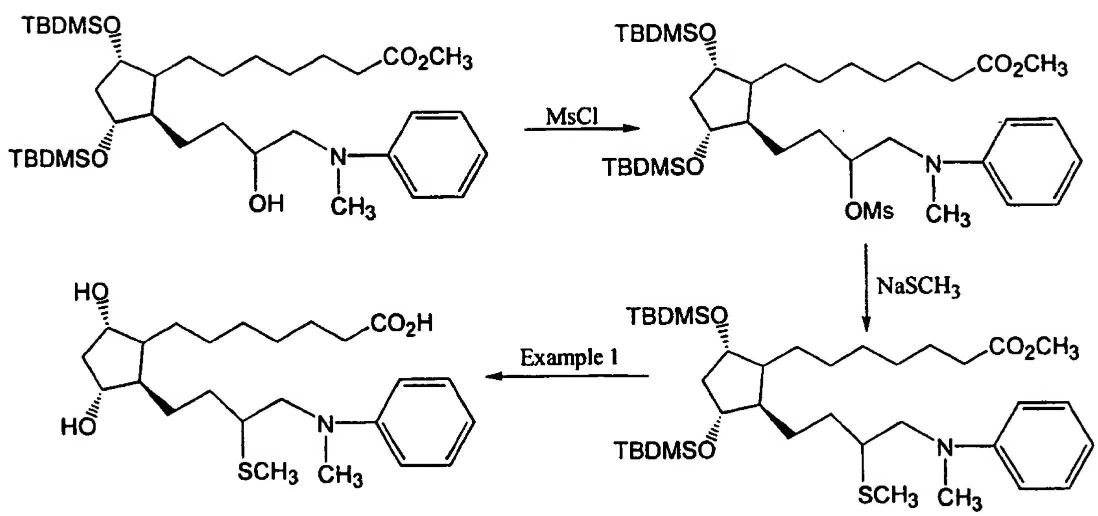
Example 32

13,14-dihydro-15-methyl-16-(2-methylphenylthio) tetranor Prostaglandin F1 α 1-N-methanesulfonamide



Example 33

Preparation of 13,14-dihydro-15-methylthio-15-dehydroxy-16-(N-methylphenylamino) tetranor Prostaglandin F1α:

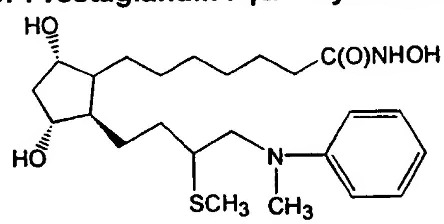


The appropriate bis-silylated compound synthesized in **Example 1** is treated with methanesulfonyl chloride (1.2 equiv.) and base (1.2 equiv.) as described in the following references: E.J. Corey et al., "Simple Stereospecific Routes to 9-epi-Prostaglandin $F_2\alpha$", J.C.S. Chem. Comm. (1975) p. 658-9; E.J. Corey et al., "Superoxide ion as a Synthetically Useful Oxygen Nucleophile", Tetrahedron Lett. (1975) p. 3183-6; and references cited therein, to generate the intermediate mesylate, which is then treated immediately with nucleophiles (sodium thiomethoxide) as described in E.J. Corey et al., "Total Synthesis of 5-desoxy Leukotriene D. A New and Useful Equivalent of the 4-Formyl-Trans,Trans-1,3-Butadienyl Anion", Tetrahedron Lett. Vol. 23 (1982) p. 3463-66, and references cited therein, to give 13,14-dihydro-15-methylthio-15-dehydroxy-16-(N-methylphenylamino) tetranor Prostaglandin $F_1\alpha$ after deprotection as described in **Example 1**.

Examples 34-36 are prepared using substantially the same procedure as that described in **Example 33** (using the appropriate derivative of **Formula IV**). The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.

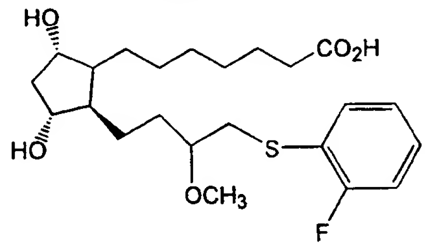
Example 34

13,14-dihydro-15-methylthio-15-dehydroxy-16-(N-methyl-phenylamino) tetranor Prostaglandin $F_1\alpha$ 1-hydroxamic acid



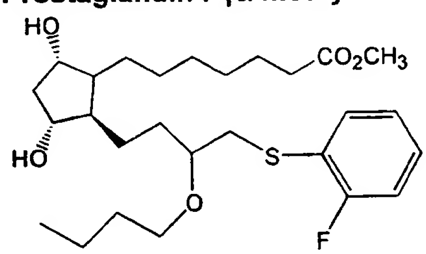
Example 35

13,14-dihydro-15-methoxy-15-dehydroxy-16-(2-fluorophenylthio) tetranor Prostaglandin F$_{1}\alpha$



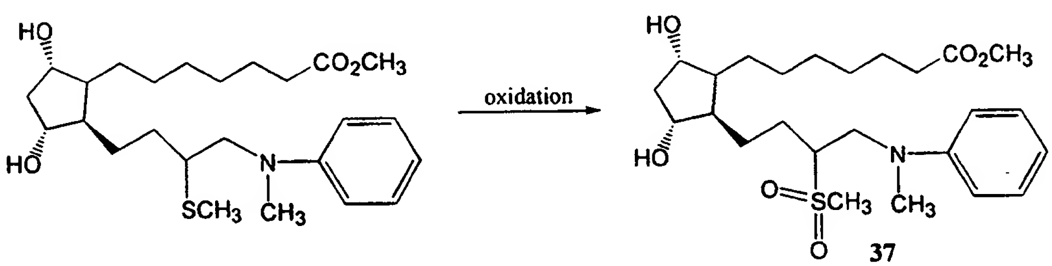
Example 36

13,14-dihydro-15-butoxy-15-dehydroxy-16-(phenylthio) tetranor Prostaglandin F$_{1}\alpha$ methyl ester



Example 37

Preparation of 13,14-dihydro-15-sulfonylmethyl-15-dehydroxy-16-(N-methyl-phenylamino) tetranor Prostaglandin F$_{1}\alpha$ methyl ester:



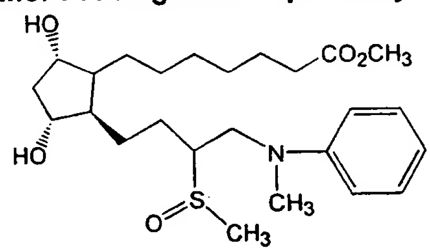
37

The methyl ester is treated with the appropriate oxidizing agent as described in the following references: E.J. Corey et al., "Total Synthesis of 5-desoxy Leukotriene D. A New and Useful Equivalent of the 4-Formyl-Trans,Trans-1,3-Butadienyl Anion", Tetrahedron Lett. Vol. 23 (1982) p. 3463-66; Prostaglandins Vol. 24 (1982) p. 801; Y. Girard et al., "Synthesis of the Sulfones of Leukotrienes C_4, D_4, and E_4", Tetrahedron Lett. Vol. 23 (1982) p. 1023-26; and references cited therein, or as described in **Example 23**.

Example 38 is prepared using substantially the same procedure as that described in **Example 37** (using the appropriate derivative of **Formula V**). The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.

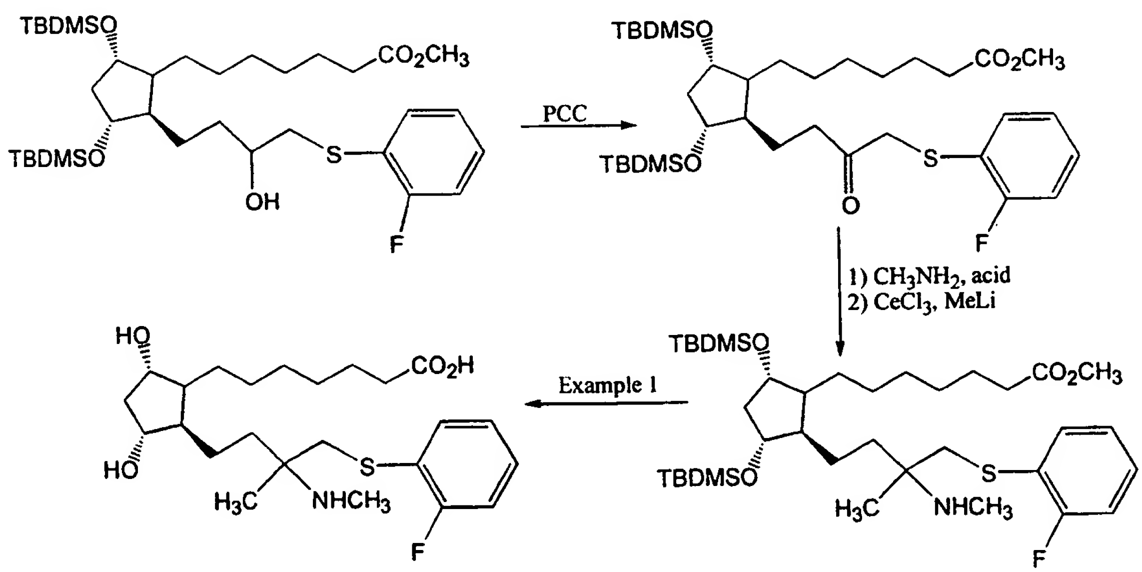
Example 38

13,14-dihydro-15-sulfoxylmethyl-15-dehydroxy-16-(N-methyl-phenylamino) tetranor Prostaglandin F$_{1\alpha}$ methyl ester



Example 39

Preparation of 13,14-dihydro-15-methyl-15-aminomethyl-16-(2-fluorophenylthio) tetranor Prostaglandin F$_{1\alpha}$:



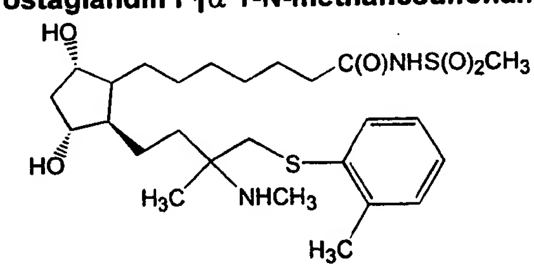
The appropriately protected derivative from **Example 8** is oxidized to the ketone as described in the following references: A. McKillop and D.W. Young, "Organic

Synthesis Using Supported Reagents - Part 1", Synthesis (1979) p. 401-22; E.J. Corey and J.W. Suggs, "Pyridinium Chlorochromate: An Efficient Reagent for Oxidation of Primary and Secondary Alcohols to Carbonyl Compounds", Tetrahedron Lett. Vol. 31 (1975) p. 2647-50; and references cited therein, and then condensed with N-methylamine to give the imine. Addition of the methylcerium nucleophile (~1.5 equiv.) (for examples of cerium chloride-mediated nucleophilic addition see: T. Imamoto, et al., "Carbon-Carbon Bond Forming Reactions Using Cerium Metal or Organcerium (III) Reagents", J. Org. Chem. Vol. 49 (1984) p. 3904-12; T. Imamoto, et al., "Reactions of Carbonyl Compounds with Grignard Reagents in the Presence of Cerium Chloride", J. Am. Chem. Soc. Vol. 111 (1989) p. 4392-98; and references cited therein) gives the aminomethyl derivative, which is then transformed as described in **Example 1** to give 13,14-dihydro-15-methyl-15-aminomethyl-16-(2-fluorophenylthio) tetranor Prostaglandin $F_{1}\alpha$.

Examples 40-42 are prepared using substantially the same procedure as that described in **Example 39** (using the appropriate derivative of **Formula I**). The skilled artisan may change temperature, pressure, atmosphere, solvents or the order of reactions as appropriate. Additionally, the skilled artisan may use protecting groups to block side reactions or increase yields as appropriate. All such modifications can readily be carried out by the skilled artisan in the art of organic chemistry, and thus are within the scope of the invention.

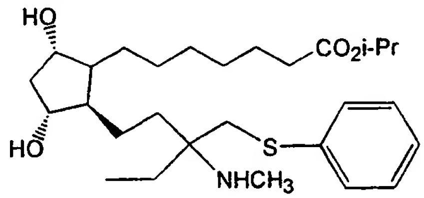
Example 40

13,14-dihydro-15-methyl-15-aminomethyl-16-(2-methylphenylthio) tetranor Prostaglandin $F_{1}\alpha$ 1-N-methanesulfonamide



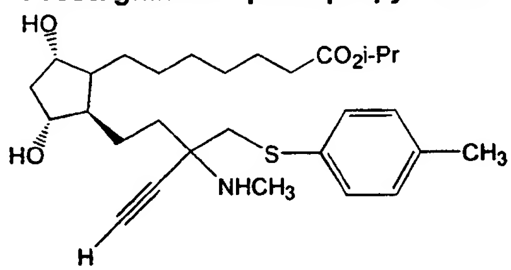
Example 41

13,14-dihydro-15-ethyl-15-aminomethyl-16-(phenylthio) tetranor Prostaglandin $F_{1}\alpha$ isopropyl ester



Example 42

13,14-dihydro-15-ethynyl-15-aminomethyl-16-(4-methylphenylthio) tetranor Prostaglandin $F_{1}\alpha$ isopropyl ester



Compositions

Compositions of the subject invention comprise a safe and effective amount of the subject compounds, and a pharmaceutically-acceptable carrier. As used herein, "safe and effective amount" means an amount of a compound sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A safe and effective amount of a compound will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

In addition to the compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a subject. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical

efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the subject being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as cornstarch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid, magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the Tweens®; wetting agents such as sodium lauryl sulfate; coloring agents; flavoring agents, excipients; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with a compound is basically determined by the way the compound is to be administered. The compounds of the present invention may be administered systemically. Routes of administration include transdermal; oral; parenterally, including subcutaneous or intravenous injection; topical; and/or intranasal.

The appropriate amount of the compound to be used may be determined by routine experimentation with animal models. Such models include, but are not limited to the intact and ovariectomized rat models, the ferret, canine, and non human primate models as well as disuse models.

Preferred unit dosage forms for injection include sterile solutions of water, physiological saline, or mixtures thereof. The pH of said solutions should be adjusted to about 7.4. Suitable carriers for injection or surgical implants include hydrogels, controlled- or sustained release devises, polylactic acid, and collagen matrices.

Suitable pharmaceutically-acceptable carriers for topical application include those suited for use in lotions, creams, gels and the like. If the compound is to be administered perorally, the preferred unit dosage form is tablets, capsules and the like. The pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Their selection will depend on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be made without difficulty by those skilled in the art.

Methods of Use

The compounds of the present invention are useful in treating many medical disorders, including for example, ocular disorders, hypertension, fertility control, nasal congestion, neurogenic bladder disorder, gastrointestinal disorders, dermatological disorders, and osteoporosis.

The compounds of the present invention are useful in increasing bone volume and trabecular number through formation of new trabeculae, increasing bone mass while maintaining a normalized bone turnover rate, and formation of bone at the endosteal surface without removing bone from the existing cortex. Thus, these compounds are useful in the treatment and prevention of bone disorders.

The preferred routes of administration for treating bone disorders are transdermal and intranasal. Other preferred routes of administration include rectal, sublingual, and oral.

The dosage range of the compound for systemic administration is from about 0.01 to about 1000 μg/kg body weight, preferably from about 0.1 to about 100 μg/kg per body weight, most preferably from about 1 to about 50 μg/kg body weight per day. The transdermal dosages will be designed to attain similar serum or plasma levels, based upon techniques known to those skilled in the art of pharmacokinetics and transdermal formulations. Plasma levels for systemic administration are expected to be in the range of 0.01 to 100 nanograms/ml, more preferably from 0.05 to 50 ng/ml, and most preferably from 0.1 to 10 ng/ml. While these dosages are based upon a daily administration rate, weekly or monthly accumulated dosages may also be used to calculate the clinical requirements.

Dosages may be varied based on the patient being treated, the condition being treated, the severity of the condition being treated, the route of administration, etc. to achieve the desired effect.

The compounds of the present invention are also useful in decreasing intraocular pressure. Thus, these compounds are useful in the treatment of glaucoma. The preferred route of administration for treating glaucoma is topically.

Composition and Method Examples

The following non-limiting examples illustrate the subject invention. The following composition and method examples do not limit the invention, but provide guidance to the skilled artisan to prepare and use the compounds, compositions and methods of the invention. In each case other compounds within the invention may be substituted for the example compound shown below with similar results. The skilled practitioner will

appreciate that the examples provide guidance and may be varied based on the condition being treated and the patient.

Example A

Pharmaceutical compositions in the form of tablets are prepared by conventional methods, such as mixing and direct compaction, formulated as follows:

Ingredient	Quantity (mg per tablet)
Compound of Example 20	5
Microcrystalline Cellulose	100
Sodium Starch Glycollate	30
Magnesium Stearate	3

When administered orally once daily, the above composition substantially increases bone volume in a patient suffering from osteoporosis.

Example B

Pharmaceutical compositions in liquid form are prepared by conventional methods, formulated as follows:

Ingredient	Quantity
Compound of Example 20	5 mg
Phosphate buffered physiological saline	10 ml
Methyl Paraben	0.05ml

When 1.0 ml of the above composition is administered subcutaneously once daily, the above composition substantially increases bone volume in a patient suffering from osteoporosis.

Example C

Topical pharmaceutical compositions for lowering intraocular pressure are prepared by conventional methods and formulated as follows:

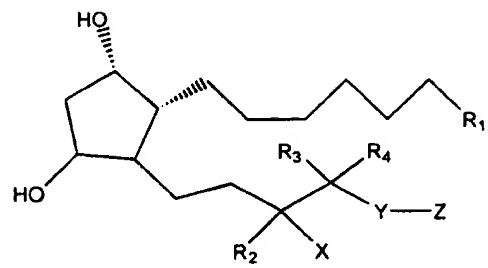
Ingredient	Amount (wt %)
Compound of Example 42	0.004
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.3
Sodium Chloride	0.77
Potassium chloride	0.12
Disodium EDTA (Edetate disodium)	0.05

Benzalkonium chloride	0.01
HCL and/or NaOH	pH 7.2-7.5
Purified water	q.s. to 100%

While particular embodiments of the subject invention have been described, it would be obvious to those skilled in the art that various changes and modifications to the compositions disclosed herein can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

What is claimed is:

1. A compound having the structure:



characterized in that

(a) R_1 is CO_2H, C(O)NHOH, CO_2R_5, CH_2OH, $S(O)_2R_5$, $C(O)NHR_5$, $C(O)NHS(O)_2R_5$, or tetrazole; characterized in that R_5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

(b) R_2 is H or lower alkyl;

(c) X is NR_6R_7, OR_8, SR_9, $S(O)R_9$, or $S(O)_2R_9$; characterized in that R_6, R_7, and R_8 are independently selected from the group consisting of H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and characterized in that R_9 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

(d) R_3 and R_4 are independently selected from the group consisting of H, CH_3, and C_2H_5;

(e) Y is NR_{10}, S, S(O), or $S(O)_2$; characterized in that R_{10} is H, acyl, alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

(f) Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and

any optical isomer, diastereomer, enantiomer of the above structure or a pharmaceutically-acceptable salt, or biohydrolyzable amide, ester, or imide thereof.

2. The compound according to Claim 1 characterized in that R_1 is selected from the group consisting of CO_2H, C(O)NHOH, CO_2CH_3, and $CO_2C_3H_7$.

3. The compound according to Claim 2 characterized in that R_2 is H or CH_3.

4, The compound according to Claim 3 characterized in that X is OH, and Y is S or NH.

5. The compound according to Claim 4 characterized in that Z is thienyl or phenyl.

6. The compound according to any of the preceding claims characterized in that Z is substituted, said substituents being independently selected from the group consisting of halo, alkyl, haloalkyl, cyano, nitro, alkoxy, phenyl, and phenoxy.

7. The compound according to any of the preceding claims characterized in that Z is substituted; said substituents being halo or alkyl.

8. The use of a compound according to any of the preceding claims in the manufacture of a medicament for treating a bone disorder in a human or other mammal.

9. The use of Claim 8 characterized in that said bone disorder is osteoporosis.

International Application No
PCT/US 98/18339

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C405/00 //A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 26 05 584 A (ONO PHARMACEUTICAL CO) 26 August 1976 see claims	1-7
P,A	US 5 703 108 A (ROSATI ROBERT L ET AL) 30 December 1997 see claims	1,8,9
A	US 4 621 100 A (LUND JOHN E ET AL) 4 November 1986	1,8,9
A	WO 97 23225 A (ALCON LAB INC) 3 July 1997 see page 16, line 7 - page 17, line 3	1-9

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 1998	03/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Berte, M

INTERNATIONAL SEARCH REPORT

Inter. .onal Application No
PCT/US 98/18339

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